

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
30 January 2003 (30.01.2003)

PCT

(10) International Publication Number
WO 03/007919 A1

- (51) International Patent Classification⁷: **A61K 9/36**
- (21) International Application Number: PCT/GB02/03286
- (22) International Filing Date: 18 July 2002 (18.07.2002)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
0117618.9 19 July 2001 (19.07.2001) GB
- (71) Applicant (*for all designated States except US*): **PHOQUIS LIMITED** [GB/GB]; 10 Kings Hill Avenue, Kings Hill, West Malling, Kent ME19 4PQ (GB).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): **LANGRIDGE, John, Richard** [GB/GB]; Yale Cottage, The Pant, Llandegla, Denbighshire LL11 3AE (GB). **COLLINS, Janine, Clare** [GB/GB]; 28 Pennycress Road, Saxon View, Minster, Kent, ME12 3AN (GB). **TIAN, Wei** [GB/GB]; Grey Gables, 53 School Lane, Little Melton, Norfolk NR9 3AE (GB).
- (74) Agent: **BOWMAN, Paul, Alan**; Lloyd Wise, Tregear & Co., Commonwealth House, 1-19 New Oxford Street, London WC1A 1LW (GB).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: CONTROLLED DRUG DELIVERY SYSTEMS PROVIDING VARIABLE RELEASE RATES

(57) Abstract: A controlled release dosage form with variable release rates comprising: 1) a bilayer or multilayer tablet core in which at least one of the layers contains one or more pharmaceutically active ingredients and at least one of the layers contains one or more rate controlling polymers; 2) a substantially insoluble casing extended over the tablet core covering the majority of tablet surface but leaving a portion of one layer of the table core exposed (exposed layer), the casing resulting from electrostatic deposition of a powder comprising fusible particles onto the tablet core and fusing the particles to form a thin film.

WO 03/007919 A1

CONTROLLED DRUG DELIVERY SYSTEMS PROVIDING VARIABLE
RELEASE RATES

- 5 The present invention relates to a drug delivery system that releases one or more active materials at controlled and variable rates into a biological fluid, in particular, the fluid of the gastrointestinal tract.

Tablets are often the preferred means of administering medicine to a patient.

- 10 A conventional immediate release tablet releases the drug active in the body, rapidly reaching a maximum concentration then decaying expeditiously until the next administration. This method often leads to the peaks and troughs of drug concentration in the blood and requires frequent administration of tablets. Consequently, this could lead to either exacerbated harmful side
- 15 effects at high concentrations or diminished therapeutic effects at low concentrations. These effects can become acute with actives of relatively short biological half life. Another disadvantage of immediate release dosage form is that a frequent dosing regime is required, thereby causing problems of patient compliance. To counter these, controlled release dosage forms that
- 20 release actives at a constant rate over a defined period of time (zero order release) have been frequently employed. A range of matrix forming natural and synthetic polymers is employed to prolong drug release, for example, xanthan gum, galactomannan polymers, alginate, cellulose derivatives (methycellulose, hydroxypropylcellulose and hydroxy propyl methyl cellulose
- 25 etc.), acrylic and methacrylic co-polymers and combinations thereof. The diverse range of polymers enables formulators to obtain the desired release

profile of drug actives despite the vast differences in the physicochemical properties of these actives.

- More recently, the roles of circadian rhythms in certain physiological functions
- 5 have gained increased recognition. It is known that many symptoms and onset of disease occur during specific time periods of the day, for example, gout, gall bladder and peptic ulcer attacks are most frequent at night; angina pectoris, sudden cardiac death, ventricular arrhythmia, stroke all occur most frequently in the morning (Smolensky, M. H. (2001), CNS Spectrum, Volume
- 10 16, Pages 467 – 482). This knowledge has led to the development of chronotherapeutics that requires a more “programmable” release of drug in the human body to enhance the therapeutic effect and to minimise the adverse effects of the drug.
- 15 GB2241485 claims a pulsed release device for releasing the contents of a capsule into an aqueous medium that comprises a water impermeable capsule having at least one orifice which is characterised in that the orifice is closed with a water soluble or water dispersible plug.
- 20 US6303144 discloses a controlled release preparation containing at least one kind of a pharmaceutically active ingredient, a male piece and a female piece, the pieces fitting together to enclose the active substance therein, wherein the male piece is made from a material that gels in the intestinal juice.

US464633 claims a pharmaceutical tablet for oral administration suitable to release the active substance after a definite period of time, consisting essentially of: a core containing the active substance and a polymeric substance which swells and/or gels and/or erodes on contact with water; a
5 layer applied externally to said core by a compression process with a thickness of 0.2 – 4.5 mm which allows the release of said active after 2- 3 hours.

US 6183778 claims an oral dosage form in the form of a tablet, capable of
10 providing one or more pharmaceutically active substances in two or more different releases, the dosage form comprising at least three layers of specific geometric shape, wherein the dosage form comprises: a) a first layer, from which there occurs a first release of at least one pharmaceutically active substance, wherein the release is characterised as an immediate release or a
15 controlled release, the layer comprising substances which swell or solubilise when contacted with aqueous liquids; b) a second layer from which there occurs a second release of at least one pharmaceutically active substances, wherein at least one pharmaceutically active substance is the same as or different from the at least one pharmaceutically active substance released
20 from the first layer in the first release, wherein the second release is characterised as controlled release, the second layer comprising substances that swell, or erode, or are gellable when contacted with aqueous liquid; and
c) a third layer at least partially coating one or more free surfaces of the second layer, the third layer comprising substances that swell, or erode, or
25 are gellable when contacted with aqueous liquid.

US5681583 discloses a multilayered controlled-release solid pharmaceutical composition in tablet form suitable for oral administration comprising at least two layers containing active material in association with excipients and
5 additives. One layer of the tablet releases a portion of the drug quickly while the other layer and optionally further layers release portions of the drug more gradually.

US 5213808 discloses an article for controlled delivery of an active substance
10 into an aqueous phase has a first layer containing an active substance, and a second layer of a crystalline polymer matrix and a non-ionic surface active agent, the second layer also containing the same or different active substance substantially homogeneously dispersed therein. The article enables release of a drug active at a constant plateau level followed by a pulse of drug after a
15 predetermined time.

US5004614 discloses controlled release devices having a core including an active agent and an outer coating which is substantially impermeable to the entrance of an environmental fluid and substantially impermeable to the
20 release of the active agent during a dispensing period allow the controlled release of the active agent through an orifice in the outer coating. The coating thickness, the position, number and the sizes of the orifices are the key variables influencing the release profile.

WO 921445 discloses that electrostatic deposition may be used to apply a coating of controlled thickness and may be employed for a medicinal product containing a drug that is to be instantaneously released when administered or that is to be the subject of controlled or modulated release, such control of modulation being achieved from the nature of the coating and/or from the nature of core. Where the desired form of release is to be achieved by characteristics of the coating, it may be preferred to leave one portion of the product uncoated or coated with different material. In the case of a tablet having faces at opposite ends connected by a cylinder side wall, the portion that is uncoated or coated with different material may be one of the faces of the tablet, a small portion of one of the faces or a side wall of the tablets. However, there is no disclosure as to whether or how variable release rates profile can be achieved.

15

In accordance with the present invention there is provided controlled release dosage form with variable release rates comprising:

1) a bilayer or multilayer tablet core in which at least one of the layers contains one or more pharmaceutically active ingredients and one or more of the layers contains one or more rate controlling polymers

20

2) a substantially insoluble casing extended over the tablet core covering the majority of tablet surface but leaving a portion of one layer of the tablet core exposed, the casing resulting from electrostatic deposition of a

powder comprising fusible particles onto the tablet core and fusing the particles to form a thin film.

The invention provides a simple and effective means of producing a
5 pharmaceutical dosage form having variable release rate profiles for one or more pharmaceutical active agents.

It has been surprisingly found that a pharmaceutical dosage form having controlled release of an active ingredient at variable rates can be obtained by
10 electrostatic application of a thin film on the selected surface of a bilayer or multilayer tablet. Furthermore, there are no needs for a specially designed geometric shape, the mechanical removal of a portion of film coating at a defined position with a defined surface area, or the presence of specific matrix forming polymers.

15

The release profile of an active ingredient from the electrostatically coated tablets does not require the application of a thick film nor rely on the controlled thickness so long as a complete and uniform coating within the defined area is obtained.

20

The release profile of a pharmaceutical active can be determined by standard US Pharmacopoeia method using either a basket stirring element (apparatus I) or a paddle stirring element (apparatus II). VankelTM 7000 dissolution
25 apparatus (Apparatus II) was used for the present invention. The assembly

- consists of the following: a covered vessel made of glass or other inert, transparent material; a motor; a paddle formed from a blade and a shaft. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly without significant wobble. The
- 5 vertical centre line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The distance of 25 ± 2 mm between the paddle and the inside bottom of the vessel is maintained during the test.
- 10 The vessel is partially immersed in a suitable waterbath which maintains the temperature inside the vessel at $37 \pm 0.5^\circ\text{C}$ during the test and keeping the bath fluid in constant, smooth motion. The vessel is cylindrical, with a hemispherical bottom. Its sides are flanged at the top. A fitted cover may be used to retard evaporation. Demineralised water is added to the vessel. The
- 15 dosage unit (one single tablet) is allowed to sink to the bottom of the vessel before the rotation of the blade is started. The stirring rate is set at 50 rpm. The released active ingredient with time is measured by a suitable means e.g. u.v. analysis, HPLC etc. and expressed as percentage release (w/w) of the total weight of active ingredient.
- 20
- In one embodiment according to the present invention the pharmaceutical dosage form has increased release rates over a definite period of time, where the exposed layer contains a lower amount of active material and/or has a slower release rate than the enclosed layer. The pharmaceutical dosage form
- 25 may release its active ingredient over a prolonged period of time. Preferably a

substantially complete release (i.e. 70%) of the pharmaceutical active ingredient is achieved after at least 4 hours. More preferably, a substantially complete release (i.e. 70%) of the pharmaceutical active is achieved after 6 hours.

5

The pharmaceutical dosage form releases the active ingredient over a first period at a slower rate than a subsequent second period. Preferably, the release rate during the second period is at least 50% greater than the first period; more preferably, the release rate during the second period is at least 75% greater than the first period. Preferably, the first period extends to at least 1 hour; more preferably the first period extends to at least 2 hours.

In a further embodiment of the invention the pharmaceutical dosage form has a delayed release profile over a definite period of time, where the exposed layer contains no active material, but contains one or more rate controlling polymers. Preferably, substantially no active ingredient, e.g. less than 10% of the active ingredient is released after at least 1 hour; more preferably less than 10% of the active ingredient is released after at least 2 hours.

In a further embodiment of the invention the pharmaceutical dosage form initially releases a first pharmaceutically active agent at a rapid release rate (fast phase), followed by the release of the same or second pharmaceutically active agent or at a slower rate, where the exposed layer contains one or more active ingredients, which can be the same or different from the active ingredient (s) present in the enclosed layer and one or more rate controlling

polymers are present in the enclosed layer, but are absent in the exposed layer. Preferably the release of the first ingredient or the fast release phase is substantially completed within 40% of the entire dissolution period; more preferably, the release of the first ingredient or the fast release phase is

5 substantially completed within 30% of the entire dissolution period.

The casing extending over the tablet core results from the electrostatic deposition of a powder comprising fusible particles. This technique allows the formation of a thin, continuous casing over the tablet core. Although the

10 release profile does not depend on the coating thickness, it is of importance that a continuous and complete coverage is applied in order to minimise pore formation. Typically this requires the deposition of several layers of powdered material (the powders have a mean diameter of 10 μm) to give a coating thickness of at least 20 μm after fusion. Generally the average thickness of

15 the casing is in the range 20 to 50 μm . In general, the casing will cover from 0 to 99% of the surface area of the exposed layer. Generally the coating results in a weight gain of less than 5%, often less than 4% and frequently less than 3% by weight of the tablet core.

20 The shape of the tablet core is not critical since the electrostatic deposition of powder can readily be achieved over a variety of shaped bodies. The tablet core is conveniently formed by conventional tableting techniques e.g. compression of powder and/or granules, although other moulding techniques may be employed. A convenient tablet core has a circular cross-section and

25 two major opposing surfaces which may be, for example, planar, planar with a bevelled edge, concave, convex etc. The insoluble casing may conveniently

extend over one of the major surfaces and the side wall leaving the other major surface exposed.

The tablet core comprises at least one adjuvant and a pharmaceutically active ingredient. Generally the adjuvant will comprise a binder. Suitable binders are well known and include acacia, alginic acid, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydrogenated vegetable oil, hydroxypropylmethylcellulose, magnesium aluminium silicate, maltodextrin, methylcellulose, polyethylene oxide, povidone, sodium alginate and hydrogenated vegetable oils.

The tablet core preferably comprises a release rate controlling additive. For example, the drug may be held within a hydrophobic polymer matrix so that it is gradually leached out of the matrix upon contact with body fluids. Alternatively, the drug may be held within a hydrophilic matrix which gradually dissolves in the presence of body fluid.

Suitable release rate controlling polymers include polymethacrylates, ethylcellulose, hydroxypropylmethylcellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid polymer, polyethylene glycol, polyethylene oxide, carrageenan, cellulose acetate, zein etc.

The tablet core may comprise other conventional tableting ingredients, including diluents, disintegrants, lubricants, wetting agents, glidants, surfactants, release aids, colourants, gas producers, etc.

Suitable diluents include lactose, cellulose, dicalcium phosphate, sucrose, 5 dextrose, fructose, xylitol, mannitol, sorbitol, calcium sulphate, starches, calcium carbonate, sodium carbonate, dextrates, dextrin, kaolin, lactitol, magnesium carbonate, magnesium oxide, maltitol, maltodextrin and maltose. Suitable lubricants include magnesium stearate and sodium stearyl fumarate. Suitable glidants include colloidal silica and talc.

10

Suitable wetting agents include sodium lauryl sulphate and docusate sodium. Suitable gas producers include sodium bicarbonate and citric acid.

The pharmaceutically active ingredient may be selected from a wide range of 15 substances which may be administered orally. Suitable ingredients include acid-peptic and motility influencing agents, laxatives antidiarrhoeals, colorectal agents, pancreatic enzymes and bile acids, antiarrhythmics, antianginals, diuretics, anti-hypertensives, anti-coagulants, anti-thrombotics, fibrinolytics, haemostatics, hypolipidaemic agents, anti-anaemia and 20 neurotropaemia agents, hypnotics, anxiolytics, anti-psychotics, anti-depressants, anti-emetics, anti-convulsants, CNS stimulants, analgesics, anti-pyretics, anti-migraine agents, non-steroidal anti-inflammatory agents, anti-gout agents, muscle relaxants, neuro-muscular agents, steroids, hypoglycaemic agents, hyperglycaemic agents, diagnostic agents, antibiotics, 25 anti-fungals, anti-malarials, anti-virals, immunosuppressants, nutritional agents, vitamins, electrolytes, anorectic agents, appetite suppressants, bronchodilators, expectorants, anti-tussives, mucolytic, decongestants, anti-

glaucoma agents, oral contraceptive agents, diagnostic and neoplastic agents.

The electrostatic application of powder material to a substrate is known.

- 5 Methods have already been developed in the fields of electrophotography and electrography and examples of suitable methods are described, for example, in Electrophotography and Development Physics, Revised Second Edition, by L.B. Schein, published by Laplacian Press, Morgan Hill California. The electrostatic application of powder material to a solid dosage form is known
- 10 and techniques are disclosed, for example, in GB9929946.3, WO92/14451, WO96/35413, WO96/35516 and PCT/GB01/00425, and British Patent Application No. 9929946.3.

- For example, WO92/14451 describes a process in which the cores of
- 15 pharmaceutical tablets are conveyed on an earthed conveyor belt and electrostatically charged powder is deposited on the cores to form a powder coating on the surface of the cores.

- A powder material for electrostatic application to a substrate should have
- 20 certain properties. For example, the electrical properties of the powder material should be such as to make the powder material suitable for electrostatic application, and other properties of the powder material should be such that the material can be secured to the substrate once electrostatic application has taken place.

25

WO96/35413 describes a powder material which is especially suitable for electrostatic application to a poorly-conducting (non-metal) substrate such as a pharmaceutical tablet. Because it may be difficult to find a single

component capable of providing the powder material with all the desired properties, the powder material comprises a number of different components which together are capable of providing the material with all or at least as many as possible of the desired properties, the components being co-processed to form "composite particles". For example, the powder material may comprise composite particles including one component which is fusible to form a continuous film on the surface of the substrate, and another component which has desirable electrical properties.

10 A potential disadvantage of the above mentioned powder materials, however, is that they are not readily adaptable to changes in formulation. The formulation of a powder material may be changed for a number of different reasons. For example, if the material is a coloured material, there may be a change in the colourant, or if the material is an active material, for example a
15 physiologically active material there may be a change in the type of active material, or in the concentration of that active material. Because all the components of the powder material are intimately mixed, any change in the components will alter the material's electrical properties and hence its performance in electrostatic application. Whenever there is a change in
20 formulation, it may therefore be necessary, for optimum performance, to adjust the content of the component(s) that make the material suitable for electrostatic application, or perhaps even to use a different component.

PCT/GB01/00425 discloses a method of electrostatically applying a powder
25 material to a substrate, wherein at least some of the particles of the material comprise a core and a shell surrounding the core, the core and the shell having different physical and/or chemical properties.

Where the particles of the powder material comprise a core and a shell surrounding the core, it is possible to place those components which are likely to be altered, for example colourant in the core, and to provide a more universal shell composition which is suitable for use with various core compositions, so that alterations may be made to the components that are in the core without substantially affecting the overall suitability of the powder material; thus, the shell ensures that the change in composition of the core does not affect the performance of the material in electrostatic application. Accordingly, alterations to one component of the powder material may be made with minimum alteration in the amounts of other components.

Generally, the powder material includes a component which is fusible, and that component may be present in the shell or in the core or in both the shell and the core. Advantageously, the fusible component is treatable to form a continuous film coating. Examples of suitable components are as follows: polyacrylates, for example polymethacrylates; polyesters; polyurethanes; polyamides, for example nylons; polyureas; polysulphones; polyethers; polystyrene; polyvinylpyrrolidone; biodegradable polymers, for example polycaprolactones, polyanhydrides, polylactides, polyglycolides, polyhydroxybutyrates and polyhydroxyvalerates; sugars, for example lactitol, sorbitol xylitol, galactitol, maltitol, sucrose, dextrose, fructose, xylose and galactose; hydrophobic waxes and oils, for example vegetable oils and hydrogenated vegetable oils (saturated and unsaturated fatty acids) e.g. hydrogenated castor oil, carnauba wax, and beeswax; hydrophilic waxes; polyalkenes and polyalkene oxides; polyethylene glycol. Clearly there may be other suitable materials, and the above are given merely as examples. One or more fusible materials may be present. Preferred fusible materials generally function as a binder for other components in the powder.

In general the powder material should contain at least 30%, usually at least 35%, advantageously at least 80%, by weight of material that is fusible, and, for example, fusible material may constitute up to 95%, e.g. up to 85%, by weight of the powder. Wax, if present, is usually present in an amount of no
5 more than 6%, especially no more than 3% by weight, and especially in an amount of at least 1% by weight, for example 1 to 6%, especially to 1 to 3%, by weight of the powder material.

Of the materials mentioned above, polymer binders (also referred to as
10 resins) should especially be mentioned. Examples include polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate and methacrylate polymers, for example an ammonio-methacrylate copolymer, for example those sold under the name Eudragit.

15

Often resin will be present with a wax as an optional further fusible component in the core; the presence of a wax may, for example, be useful where fusing is to take place by a contact system for example using a heated roller, or where it is desired to provide a glossy appearance in the fused film. The fusible
20 component may comprise a polymer which is cured during the treatment, for example by irradiation with energy in the gamma, ultra violet or radio frequency bands. For example, the core may comprise thermosetting material which is liquid at room temperature and which is hardened after application to the substrate.

25

Preferably, the powder material includes a material having a charge-control function. That functionality may be incorporated into a polymer structure, as in the case of Eudragit resin mentioned above, and/or, for a faster rate of charging, may be provided by a separate charge-control additive. Material

- having a charge-control function may be present in the shell or in the core or in both shell and core. Examples of suitable charge-control agents are as follows: metal salicylates, for example zinc salicylate, magnesium salicylate and calcium salicylate; quaternary ammonium salts; benzalkonium chloride; 5 benzethonium chloride; trimethyl tetradecyl ammonium bromide (cetrimide); and cyclodextrins and their adducts. One or more charge-control agents may be used. Charge-control agent may be present, for example, in an amount of up to 10% by weight, especially at least 1% by weight, for example from 1 to 2% by weight, based on the total weight of the powder material.
- 10 The powder material may also include a flow aid. The flow aid reduces the cohesive and/or other forces between the particles of the material to improve the flowability of the powder. Suitable flow aids (which are also known as "surface additives") are, for example, as follows: colloidal silica; metal oxides, e.g. fumed titanium dioxide, zinc oxide or alumina; metal stearates, e.g. zinc, 15 magnesium or calcium stearate; talc; functional and non-functional waxes, and polymer beads, e.g. poly-methyl methacrylate beads, fluoropolymer beads and the like. Such materials may also enhance tribocharging. A mixture of flow aids, for example silica and titanium dioxide, should especially be mentioned. The powder material may contain, for example, 0 to 3% by 20 weight, advantageously at least 0.1%, e.g. 0.2 to 2.5%, of surface additive flow aid.

- Often the powder material includes a colourant and/or an opacifier. When the powder comprises a core and shell such components are preferably present 25 in the core. Examples of suitable colourants and opacifiers are as follows: metal oxides, e.g. titanium dioxide, iron oxides; aluminium lakes, for example, indigo carmine, sunset yellow and tartrazine; approved food dyes; natural pigments. A mixture of such materials may be used if desired. Opacifier preferably constitutes no more than 50%, especially no more than 40%, more 30 especially no more than 30%, for example no more than 10% by weight of the powder material, and may be used, for example, in an amount of at least 5%

by weight of the powder. Titanium dioxide is an especially useful opacifier, providing white colour and having good hiding power and tinctorial strength. Colourant present with opacifier may, for example, constitute no more than 10%, preferably from 1 to 5%, by weight of the powder. If there is no
5 opacifier, the colourant may be, for example, 1 to 15%, e.g. 2 to 15%, especially 2 to 10%, by weight of the powder. To achieve optimum colour, amounts of up to 40% by weight of colourant may be needed in some cases, for example if inorganic pigments, e.g. iron oxides, are used. However, the powder material usually contains, for example, from 0 to 25% by weight in
10 total of colourant and/or opacifier.

The powder material may also include a dispersing agent, for example a lecithin. The dispersing agent is preferably present with the colourant/opacifier (that is, preferably in the core), serving to improve the dispersion of the colourant and opacifier, more especially when titanium
15 dioxide is used. The dispersing component is preferably a surfactant which may be anionic, cationic or non-ionic, but may be another compound which would not usually be referred to as a "surfactant" but has a similar effect. The dispersing component may be a co-solvent. The dispersing component may be one or more of, for example, sodium lauryl sulphate, docusate sodium,
20 Twines (sorbitan fatty acid esters), polyoxamers and cetostearyl alcohol. Preferably, the powder material includes at least 0.5%, e.g. at least 1%, for example from 2% to 5%, by weight of dispersing component, based on the weight of the powder material. Most often it is about 10% by weight of the colourant and opacifier content.

25

The powder material may also include a plasticiser, if necessary, to provide appropriate rheological properties. A plasticiser may be present in the core and/or the shell, but usually, if present, a plasticiser is included with resin used for the core to provide appropriate rheological properties, for example for
30 preparation of the core by extrusion in a melt extruder. Examples of suitable plasticisers include polyethylene glycols, triethyl citrate, acetyltributyl citrate,

acetyltriethyl citrate, tributyl citrate, diethyl phthalate, dibutyl phthalate, dimethyl phthalate, dibutyl sebacate and glyceryl monostearate.

5 A plasticiser may be used with a resin in an amount, for example, of up to 50% by weight of the total of that resin and plasticiser, the amount depending inter alia on the particular plasticisers used. The powder may contain an amount of up to 50% by weight of plasticiser.

10 The powder coating material may further include one or more taste modifiers, for example aspartame, acesulfame K, cyclamates, saccharin, sugars and sugar alcohols or flavourings. Preferably there is no more than 5%, more preferably no more than 1%, of flavouring based on the weight of the powder material, but larger or smaller amounts may be appropriate, depending on the particular taste modifier used.

15

If desired the powder material may further include a filler or diluent. Suitable fillers and diluents are essentially inert and low cost materials with generally little effect on the colour or other properties of the powder. Examples are as follows: alginic acid; bentonite; calcium carbonate; kaolin; talc; magnesium
20 aluminium silicate; and magnesium carbonate.

The particle size of the powder material has an important effect on the behaviour of the material in electrostatic application. Although materials having a small particle size are recognised as having disadvantages such as
25 being more difficult to produce and to handle by virtue of the material's cohesiveness, such material has special benefits for electrostatic application and the benefits may more than counter the disadvantages. For example, the high surface to mass ratio provided by a small particle increase the

electrostatic forces on the particle in comparison to the inertial forces.

Increasing the force on a particle has the benefit of increasing the force that causes it to move into contact with the substrate, whilst a reduction in the inertia reduces the force needed to accelerate a particle and reduces the

- 5 likelihood of a particle arriving at the substrate bouncing back off the substrate. However, very small particle sizes may not be achievable where the coating material comprises a high proportion of a particular ingredient, for example a high proportion of active material.

- 10 Preferably, at least 50% by volume of the particles of the material have a particle size no more than 100µm. Advantageously, at least 50% by volume of the particles of the material have a particle size in the range of 5µm to 40µm. More advantageously, at least 50% by volume of the particles of the material have a particle size in the range of 10 to 25µm.

15

Powder having a narrow range of particle size should especially be mentioned. Particle size distribution may be quoted, for example, in terms of the Geometric Standard Deviation ("GSD") ratios d_{90}/d_{50} or d_{50}/d_{10} where d_{90} denotes the particle size at which 90% by volume of the particles are below

- 20 this figure (and 10% are above), d_{10} represents the particle size at which 10% by volume of the particles are below this figure (and 90% are above), and d_{50} represents the mean particle size. Advantageously, the mean (d_{50}) is in the range of from 5 to 40µm, for example, from 10 to 25µm. Preferably, d_{90}/d_{50} is no more than 1.5, especially no more than 1.35, more especially no more than 1.32, for example in the range of from 1.2 to 1.5, especially 1.25 to 1.35, more especially 1.27 to 1.32, the particle sizes being measured, for example, by Coulter Counter. Thus, for example, the powder may have $d_{50} = 10\mu\text{m}$, $d_{90} = 13\mu\text{m}$, $d_{10} = 7\mu\text{m}$, so that $d_{90}/d_{50} = 1.3$ and $d_{50}/d_{10} = 1.4$.

The powder material is fusible so that it is treatable to form a continuous film coating.

It is important that the powder can be fused or treated without degradation of any active material in the powder and without degradation of the tablet core. For some materials it may be possible for the treatment step to involve temperatures up to and above 250°C. Preferably, however, the powder material is fusible at a pressure of less than 100lb/sq. inch, preferably at atmospheric pressure, at a temperature of less than 200°C, and most commonly below 150°C, and often at least 80°C, for example in the range of from 100 to 140°C.

Fusing of the powder material may be carried out by any of a number of different fusing methods. If desired, rupture of the shell and fusing of the material may be carried out in a single step. The powder material is preferably fused by changing the temperature of the powder, for example by radiant fusing using electromagnetic radiation, for example infra red radiation or ultra-violet radiation, or conduction or induction, or by flash fusing. The amount of heat required may be reduced by applying pressure to the powder material, for example by cold pressure fusing or hot roll fusing.

Preferably, the powder material has a glass transition temperature (T_g) in the range of 40°C to 120°C. Advantageously, the material has a T_g in the range of 50°C to 100°C. A preferred minimum T_g is 55°C, and a preferred maximum T_g is 70°C. Accordingly, more advantageously, the material has a T_g in the range of 55°C to 70°C. Generally, the powder material should be heated to a temperature above its softening point, and then allowed to cool to a temperature below its T_g .

The powder material once fused is substantially insoluble, preferably completely insoluble in aqueous media at temperatures up to the body temperature. Thus, the powder material will comprise a significant amount of an insoluble material. Preferred material comprises a polymer resin selected
5 from polymethacrylates, polyvinyl alcohols and esters, cellulose and its derivatives, cellulose ethers and esters and cellulose acetate phthalate.

The electrostatic coating of the tablet core by the powder material may be conducted by any of the methods disclosed in the above referenced patents.
10 The partial coating of the tablet core may be achieved by the use of a mask. However, preferably the partial coating is achieved by coating one face and the sides of a tablet core in accordance with the first stage of coating as described in the above mentioned patents. Thereafter the electrostatically deposited powder is fused to form a tablet core having a casing covering one
15 face and the sides, leaving the other face exposed.

The invention will be illustrated by the following examples and drawings in which:

20 Figures 1a – 1c show the construction of the dosage forms according to this invention.

Figures 2-4 show the release profile of a coated bilayer tablet providing increased rate of release

25

Figure 5 shows the release profile of a coated bilayer tablet providing delayed release of salbutamol

Figure 6 shows the release profile of a coated bilayer tablet providing an initial burst followed by sustained release of salbutamol

- 5 Figures 1a to c represent cross-sections through controlled release dosage forms in accordance with the invention. The dosage forms comprise an enclosed layer (2), and exposed layer (4) and an insoluble casing (6). In Figure 1a one major surface of the exposed layer (4) is in contact with the enclosed layer (2) and the sides and a portion of the other major surface
- 10 covered by the casing (6) leaving a portion of the major surface exposed. In Figure 1b the entire surface area of a major surface of the exposed layer (4) is free of casing (6) and exposed. In Figure 1c the entire major surface of the exposed layer and an area of the side is free of casing (6) and exposed. In all these embodiments the enclosed layer (2) is surrounded by the casing (6) and
- 15 exposed layer (4).

The following materials were used in the Examples:

- | | | |
|----|----------------|---|
| | Methocel K4M | hydroxy propyl methyl cellulose commercially available from Dow Chemicals |
| 20 | Methocel K15M | hydroxy propyl methyl cellulose commercially available from Dow Chemicals |
| | Eudragit RSPO | a methacrylate copolymer commercially available from Rohm |
| | Kollidone S630 | povidone from International Speciality Products |

Example 1: Bilayer tablet having increased release rate of Salbutamol sulphate

The construction of the dosage form is shown in Figure 1b.

5 Two layer tablet cores were formulated as follows:

Exposed layer formulation:

	Salbutamol sulphate	0.69%
	Methocel K4M	15.00%
	Anhydrous lactose DC	83.30%
10	Magnesium stearate	1.00%

Enclosed layer formulation:

	Salbutamol sulphate	4.82%
	Eudragit RSPO	10.00%
	Anhydrous lactose DC	84.15%
15	Magnesium stearate	1.00%

Approximately 175 mg of the enclosed layer formulation was added to a 10 mm die of a Manesty F3 tablet press and slightly compacted with a 10 mm normal concave punch. 175 mg of the exposed layer formulation was added
20 to the die and the two layers compressed to form 10 mm normal biconvex tablets of hardness approximately 20 kp.

The coat formulation for the casing was as follows:

	84.0% Eudragit RSPO
25	8.5% polyethylene glycol 6000

5.0% titanium dioxide

2.5% sunset yellow lake.

To prepare the coating powder, the above ingredients were weighed, blended,
5 and then extruded. The extrudates were pin-milled, micronised and classified
in an air jet mill to give a median particle size of approximately 10 μm .

A blend containing 4.5% of coat formulation and 95.5% of a silicone-coated
ferrite was prepared. The tablets were coated electrostatically using the
10 coat/carrier blend in a conventional dual component delivery device adapted
from the electrophotographic industry such that the coating formulation
(without ferrite carrier) was applied to one face and the sides of the tablet
leaving the face of the exposed layer uncoated. Details of the coating process
are disclosed in British Patent Application No. 9929946.3. The coat was fused
15 onto the tablets at approximately 100°C, to provide a range of coating
thickness between 20 and 50 microns.

Six tablets were assessed for release rate in 500 ml of demineralised water at
37°C using USP apparatus II (paddles) at 50 rpm and the dissolved
20 salbutamol was analysed using reverse phase HPLC with a UV detector at
276 nm. The release rate with time is shown in Figure 2, which has evidently
demonstrated the increasing release rate profile.

It is of interest to note that the release of salbutamol largely follows biphasic
25 behaviour, i.e. an initial slow rate at approximately 3.6% per hour, followed by

a rapid release phase at 10.0% per hour representing an increase of 178% in release rate. The initial slow release phase extends to about 2 hours.

Example 2 Bilayer tablet having increased release rate of Salbutamol

5 sulphate

The construction of the dosage form is as illustrated in Figure 1b.

Two layer tablet cores were formulated as follows:

Exposed layer formulation :

10	Salbutamol sulphate	1.38%
	Methocel K15M	15.00%
	Anhydrous lactose DC	82.65%
	Magnesium stearate	1.00%

Enclosed layer formulation:

15	Salbutamol sulphate	4.13%
	Methocel K15M	10.00%
	Anhydrous lactose DC	84.85%
	Magnesium stearate	1.00%

20 Approximately 175 mg of the enclosed layer formulation was added to a 10 mm die of a Manesty F3 tablet press and slightly compacted with a 10 mm normal concave punch. 175 mg of the exposed layer formulation was added to the die and the two layers compressed to form 10 mm normal biconvex tablets of hardness approximately 20 kp.

The tablet cores were coated using the materials and method described in Example 1. The release rate with time was determined for the coated tablets using the method described in Example 1 and is shown in Figure 3.

- 5 It is evident that the electrostatic coated bilayer tablet exhibits an increased rate of release during dissolution. The release rate at the initial phase was approximately 4.5% per hour and 9.0% per hour at the later phase representing an increase of 100% in release rate. The initial release phase extends to about 3.5 hours.

10

Example 3 Bilayer tablet having increased release rate of Salbutamol sulphate

The construction of the dosage form is as shown in Figure 1b.

15

Two layer tablet cores were formulated as follows:

Exposed layer formulation:

	Salbutamol sulphate	0.54%
	Kolloidone S630	30.00%
20	Dihydrogen calcium phosphate anhydrous (DCPA)	61.86%
	Potassium chloride	5.00%
	Magnesium stearate	2.00%
	Silicon dioxide	0.50%
25	Indigo dye	0.10%

Enclosed layer formulation:

	Salbutamol sulphate	3.75%
	Kolloidone S630	10.00%
	DCPA	78.75%
5	Potassium chloride	5.00%
	Magnesium stearate	2.00%
	Silicon dioxide	0.50%

Two separate granules for the exposed layer formulation and the enclosed
10 layer formulation were prepared separately. Salbutamol sulphate, potassium
chloride and DCPA were sieved through 710 μm sieve, which were then
blended with Salbutamol sulphate and povidone S630. The blend was then
granulated with water using a Kenwood Magimix Food Processor. The wet
granules were dried in a forced air oven at 60°C to a dry matter content of
15 less than 2.0%. The granules were screened through a 710 μm sieve and
blended with dye and magnesium stearate.

Bilayer tablet cores were made by a Riva bi-layer press using 10 mm normal
concave tooling. These tablet cores were coated using the materials and
20 method described in Example 1. The release rate with time was determined
for the coated tablets using the method described in Example 1 and is shown
in Figure 4.

It is evident that the electrostatic coated bilayer tablet exhibits an increased rate of release during dissolution. The release rate at the initial phase was approximately 4.6% per hour and 8.8% per hour at the later phase representing an increase of 91% in release rate. The initial release phase
 5 extends to about 4 hours.

Example 4 Bilayer tablet having delayed release of Salbutamol sulphate

The construction of the dosage form is as shown in Figure 1b.

10

Two layer tablet cores were formulated as follows:

Exposed layer formulation:

	Salbutamol sulphate	0.00%
	Kolloidone S630	20.00%
15	DCPA	72.40%
	Potassium chloride	5.00%
	Magnesium stearate	2.00%
	Silicon dioxide	0.50%
	Indigo dye	0.10%

20 Enclosed layer formulation:

	Salbutamol sulphate	4.28%
	Kolloidone S630	20.00%
	DCPA	68.22%
	Potassium chloride	5.00%
25	Magnesium stearate	2.00%

Silicon dioxide

0.50%

Two separate granules for the exposed layer formulation and the enclosed layer formulation were prepared by the same method as described in

5 Example 3.

Bilayer tablet cores were made by a Riva bi-layer press using 10 mm normal concave tooling. These tablet cores were coated using the materials and method described in Example 1. The release rate with time was determined
10 for the coated tablets using the method described in Example 1 and is shown in Figure 5.

It is evident that the electrostatic coated bilayer tablet exhibited a delayed release of salbutamol with a lag time of approximately 3 hours. The release
15 kinetics after 3 hours can be described by the following equation (up to 82% release):

$$\% \text{ Release} = 10.0 * (t - 2.75)^{0.95}$$

Where t represents the dissolution time

Therefore, the subsequent release of salbutamol followed an approximately
20 zero order release profile (when the release exponent = 1.0).

Example 5 Bilayer tablet having an initial burst followed by a constant release profile

25 The construction of the dosage form is as shown in Figure 1b.

Two layer tablet cores were formulated as follows:

Exposed layer formulation:

	Salbutamol sulphate	2.14%
5	DCPA	42.36%
	Microcrystalline cellulose	10.00%
	Lactose DC	37.00
	PVP C15	2.00%
	Potassium chloride	5.00%
10	Magnesium stearate	1.00%
	Silicon dioxide	0.50%

Enclosed layer formulation:

	Salbutamol sulphate	2.14%
	Kolloidone S630	10.00%
15	DCPA	60.26%
	Potassium chloride	5.00%
	Magnesium stearate	2.00%
	Silicon dioxide	0.50%
	Indigo carmine lake	0.10%

20

Two separate granules for the exposed layer formulation and the enclosed layer formulation were prepared separately by the same method as described in Example 3

Bilayer tablet cores were made by a Riva bi-layer press using 10 mm normal concave tooling. These tablet cores were coated using the materials and method described in Example 1. The release rate with time was determined for the coated tablets using the method described in Example 1 and is shown in Figure 5.

It is evident that the release profile of the bilayer tablet exhibited an initial burst followed by sustained release. The release kinetics can be described by the following equations:

$$\begin{aligned} 10 \quad \% \text{ Release} &= 26.7 t^{0.58} && \text{(within the 0 – 50\% release range)} \\ \% \text{ Release} &= 50.5 + 8.75 (t - 3)^{0.85} && \text{(within the 50 – 85\% release range)} \end{aligned}$$

It is evident that the initial release follows a first order release rate (when the exponent is approximately 0.5) and the second phase of release was approximately zero order (i.e. the exponent approaching 1). The initial release phase extends to 25% of entire release period (where 100% release was achieved).

CLAIMS

1. A controlled release dosage form with variable release rates comprising:
 - 1) a bilayer or multilayer tablet core in which at least one of the
5 layers contains one or more pharmaceutically active ingredients and at least one of the layers contains one or more rate controlling polymers
 - 2) a substantially insoluble casing extended over the tablet core covering the majority of tablet surface but leaving a portion of one layer of the tablet core exposed (exposed layer), the casing resulting from electrostatic
10 deposition of a powder comprising fusible particles onto the tablet core and fusing the particles to form a thin film.
2. A controlled release dosage form as claimed in claim 1 having increased release rates over a definite period of time, in which the exposed layer contains a lower amount of active material and/or has a slower release
15 rate than the other (enclosed) layer.
3. A controlled release dosage form as claimed in Claim 2 which releases the active ingredient over a first period at a slower rate than a subsequent second period.
4. A controlled release dosage form as claimed in Claim 3 in which the
20 release rate during the second period is at least 50% greater than the first period.
5. A controlled release dosage form as claimed in Claim 4 in which more preferably the release rate during the second period is at least 75% greater than the first period.

6. A controlled release dosage form as claimed in any one of Claims 3 to 5 in which the first period extends to at least 2 hours.
7. A controlled release dosage form as claimed in Claim 1 having a delayed release profile over a definite period of time, where the exposed layer
5 contains no active material and contains one or more rate controlling polymers.
8. A controlled release dosage form as claimed in Claim 7 in which less than 10% of the active ingredient will be released in a first period of at least 1 hour.
- 10 9. A controlled release dosage form as claimed in Claim 1 which initially releases a first pharmaceutically active agent at a rapid release (fast phase) followed by the release of the same or second pharmaceutically active agent or at a slower rate in which the exposed layer is free of rate controlling polymer and contains one or more active ingredients, which can be the same
15 or different from active ingredient(s) present in the enclosed layer and one or more rate controlling polymers are present in the enclosed layer .
10. A controlled release dosage form as claimed in Claim 9 in which the fast phase is completed within 40% of the entire dissolution period of the dosage form.
- 20 11. A controlled release dosage form as claimed in any preceding claim in which at least 70% of at least one active ingredient is achieved after a period of 6 hours.
12. A controlled release pharmaceutical dosage form as claimed in any preceding claim in which the insoluble casing covers from 65 to 95% of the
25 surface area of the tablet core.

13. A controlled release pharmaceutical dosage form as claimed in any preceding claim in which the table core is formed of two layers and comprises two major opposing surfaces separated by a sidewall(s) at least one major surface and the sidewalls(s) being covered by the casing.
- 5 14. A controlled release pharmaceutical dosage form as claimed in any preceding claim in which at least one layer of the tablet core comprises a binder selected from acacia, alginic acid, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, dextrin, ethylcellulose, gelatin, glucose, guar gum, hydrogenated vegetable oil, hydroxypropylmethylcellulose
- 10 magnesium aluminium silicate, Maltodextrin, methylcellulose, polyethylene oxide, povidone, sodium alginate and hydrogenated vegetable oils.
15. A controlled release pharmaceutical dosage form as claimed in any preceding claim in which at least one layer of tablet core additionally comprises a release rate controlling polymer is selected from
- 15 polymethacrylates, ethylcellulose, hydroxypropylmethycellulose, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, calcium carboxymethylcellulose, acrylic acid polymer, polyethylene glycol, polyethylene oxide, carrageenan, cellulose acetate, and zein.
- 20 16. A controlled release pharmaceutical dosage as claimed in any preceding Claim in which at least one layer of the tablet core additionally comprises a diluent selected from lactose, cellulose, dicalcium phosphate, sucrose, dextrose, fructose, xylitol, mannitol, sorbitol, calcium sulphate, starches, calcium carbonate, sodium carbonate, dextrates, dextrin, kaolin,
- 25 lactitol, magnesium carbonate, magnesium oxide, maltitol, maltodextrin and maltose.

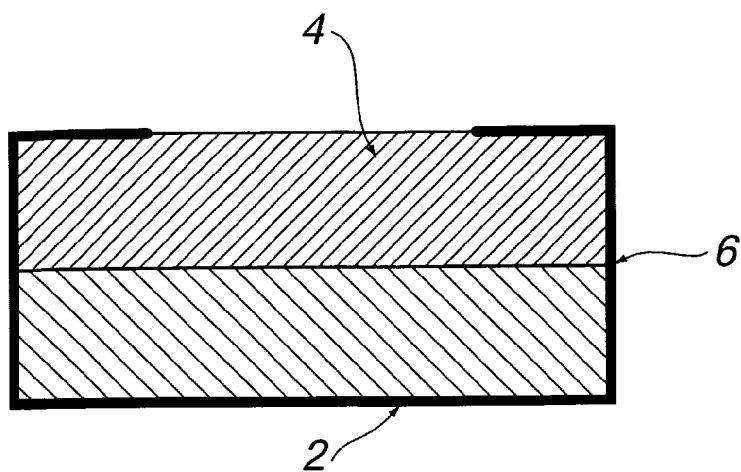
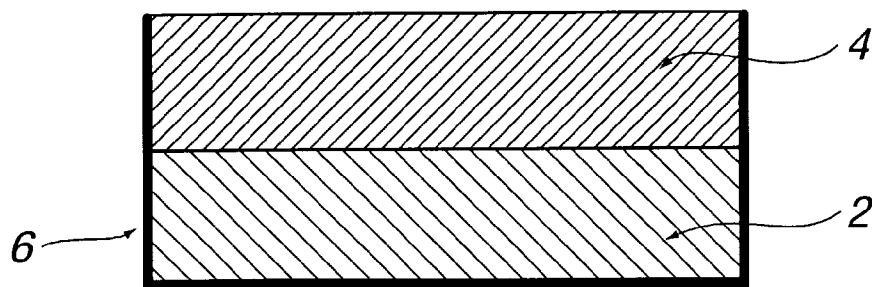
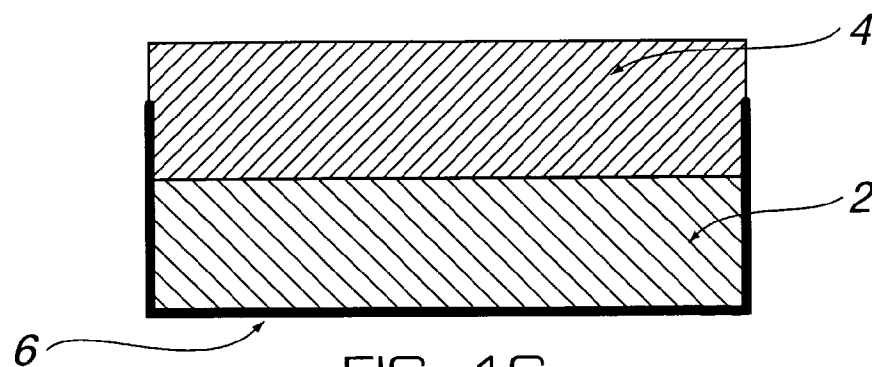
17. A controlled release pharmaceutical dosage as claimed in any preceding Claim in which at least one layer of the tablet core comprises a hydrophobic matrix, a hydrophilic matrix, or a mixture of hydrophilic and hydrophobic materials
- 5 18. A controlled release pharmaceutical dosage as claimed in any preceding claim in which the active ingredient is selected from acid-peptic and motility influencing agents, laxatives, antidiarrheals, colorectal agents, pancreatic enzymes and bile acids, antiarrhythmics, antianginals, diuretics, anti-hypertensives, anti-coagulants, anti-thrombotics, fibrinolytics,
- 10 haemostatics, hypolipidaemic agents, anti-anaemia and neurotopenia agents, hypnotics, anxiolytics, anti-psychotics, anti-depressants, anti-emetics, anti-convulsants, CNS stimulants, analgesics, anti-pyretics, anti-migraine agents, non-steroidal anti-inflammatory agents, anti-gout agents, muscle relaxants, neuro-muscular agents, steroids, hypoglycaemic agents,
- 15 hyperglycaemic agents, diagnostic agents, antibiotics, anti-fungals, anti-malarials, anti-virals, immunosuppressants, nutritional agents, vitamins, electrolytes, anorectic agents, appetite suppressants, bronchodilators, expectorants, anti-tussives, mucolytes, decongestants, anti-glaucoma agents, oral contraceptive agents, diagnostic and neoplastic agents.
- 20 19. A controlled release pharmaceutical dosage as claimed in any preceding Claim in which the casing comprises a polymer resin selected from polymethacrylates, cellulose and its derivatives, cellulose ethers and esters and cellulose acetate phthalate.
20. A controlled release pharmaceutical dosage as claimed in any
- 25 preceding Claim in which the casing additionally comprises one or more adjuvants selected from opacifiers, colourants, plasticisers, flow aids and charge control materials.
21. A controlled release pharmaceutical dosage as claimed in Claim 20 in which the casing comprises a plasticiser selected from polyethylene glycols,
- 30 triethyl citrate, acetyltributyl citrate, acetyltriethyl citrate, tributyl citrate, diethyl

phthalate, dibutyl phthalate, dimethyl phthalate, dibutyl sebacate and glyceryl monostearate.

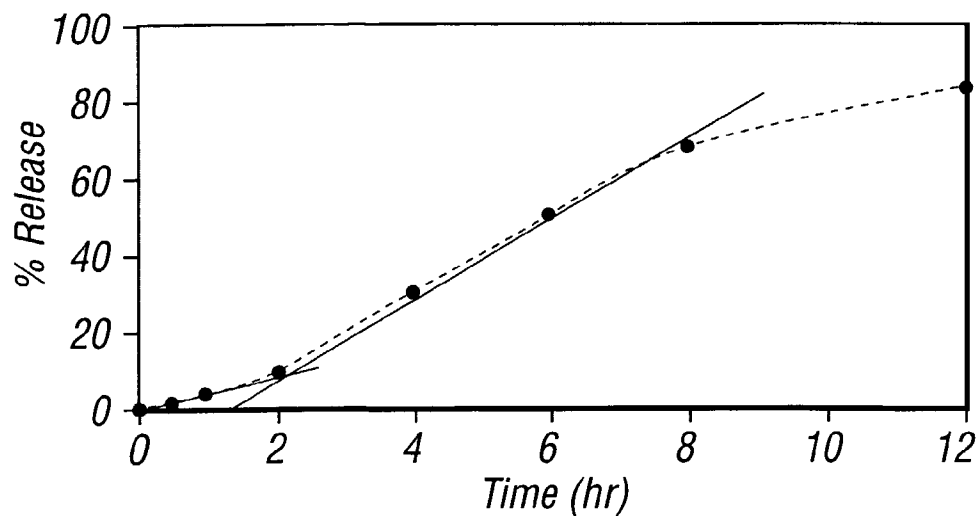
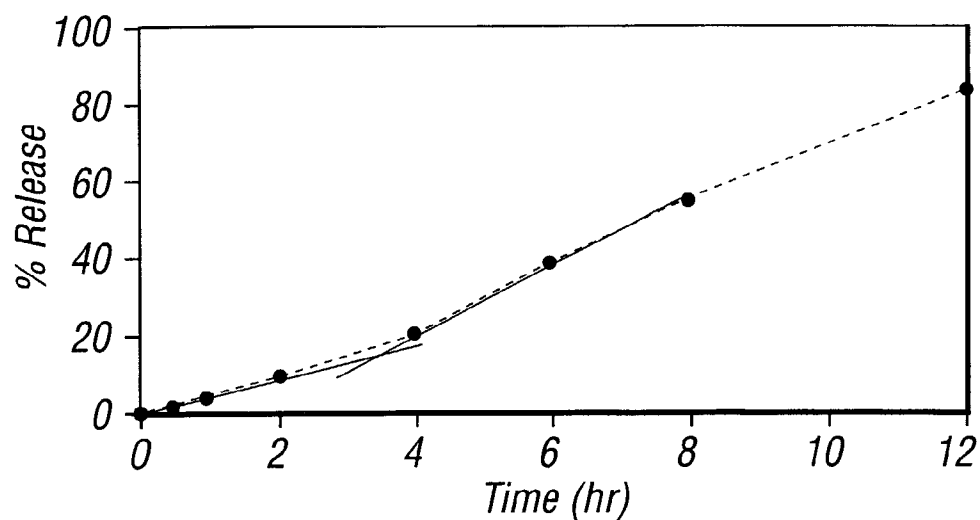
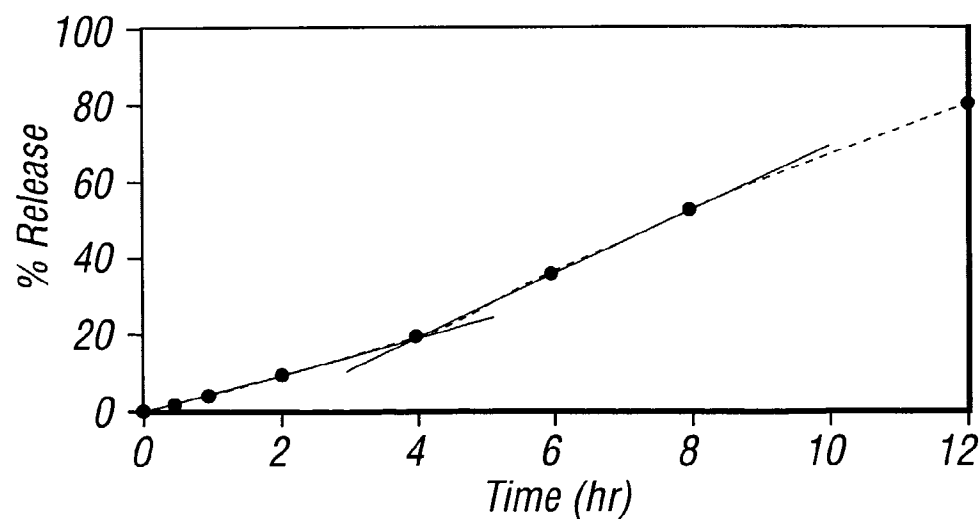
22. A controlled release pharmaceutical dosage as claimed in any preceding claim in which the casing has an average thickness of from 20 to 50 μm .

23. A controlled release pharmaceutical dosage form as claimed in any preceding claim in which the casing results in a weight gain of less than 5% by weight of the tablet core.

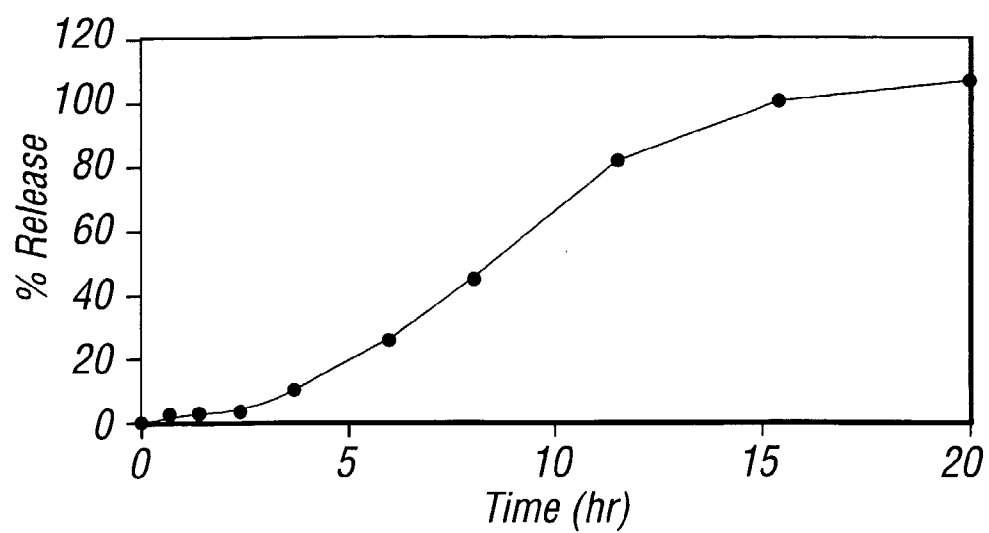
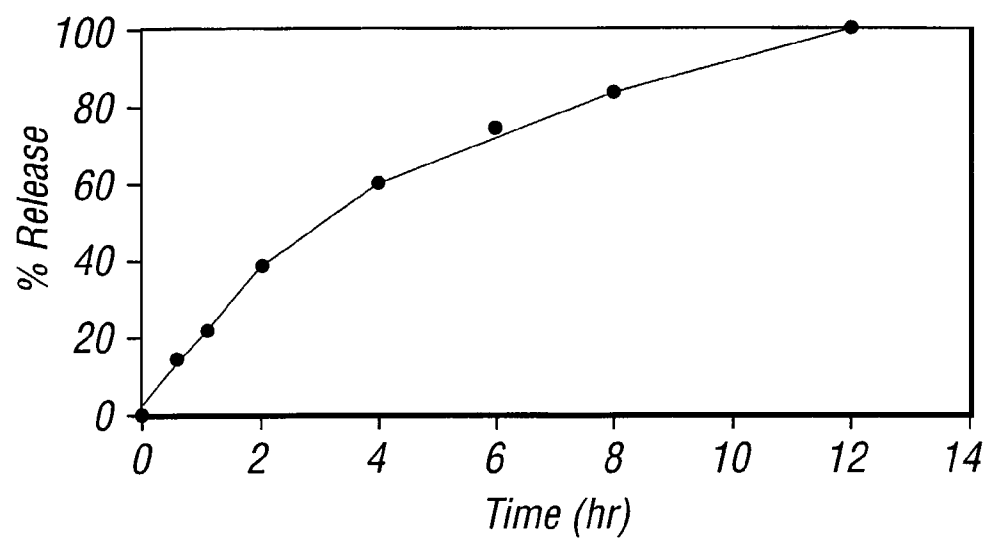
1/3

FIG. 1AFIG. 1BFIG. 1C

2/3

FIG. 2FIG. 3FIG. 4

3/3

FIG. 5FIG. 6

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03286

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 582 838 A (RORK GERALD S ET AL) 10 December 1996 (1996-12-10) column 3, line 30 - line 44 column 9, line 4 - line 21 example 1 ---	1-23
Y	US 6 117 479 A (PAGE TREVOR ET AL) 12 September 2000 (2000-09-12) column 4, line 66 -column 7, line 8 ---	1-23
Y	EP 0 365 123 B (FORUM CHEMICALS LTD) 25 April 1990 (1990-04-25) column 4, line 18 -column 5, line 5 column 7, line 37 - line 47 column 8, line 33 - line 51 column 11, line 57 -column 12, line 15 example 24 figure 18 --- -/--	1-23



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

23 October 2002

Date of mailing of the international search report

29/10/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Collura, A

INTERNATIONAL SEARCH REPORT

PCT/GB 02/03286

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 470 603 A (STANIFORTH JOHN N ET AL) 28 November 1995 (1995-11-28) column 5, line 38 - line 52 claim 24 ----	1-23
A	US 5 681 583 A (CONTE UBALDO ET AL) 28 October 1997 (1997-10-28) column 3, line 28 - line 40 claims 1,4-8,12,17 -----	1-23

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/03286

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5582838	A	10-12-1996	AU 693313 B2	25-06-1998
			AU 4472696 A	10-07-1996
			CA 2206211 A1	27-06-1996
			CN 1171048 A ,B	21-01-1998
			CZ 9701895 A3	18-02-1998
			EP 0801560 A1	22-10-1997
			FI 972586 A	17-06-1997
			HU 77370 A2	30-03-1998
			JP 11509829 T	31-08-1999
			NO 972880 A	20-06-1997
			NZ 298994 A	28-10-1998
			PL 320792 A1	27-10-1997
			RU 2168330 C2	10-06-2001
			SK 80597 A3	04-02-1998
			WO 9619201 A1	27-06-1996
US 6117479	A	12-09-2000	AU 5655196 A	29-11-1996
			AU 5655296 A	29-11-1996
			BR 9608208 A	07-12-1999
			BR 9608209 A	07-12-1999
			CA 2220485 A1	14-11-1996
			CA 2220506 A1	14-11-1996
			CN 1183738 A	03-06-1998
			CN 1183715 A	03-06-1998
			CZ 9703520 A3	15-04-1998
			CZ 9703521 A3	15-04-1998
			EP 1075838 A2	14-02-2001
			EP 0824344 A1	25-02-1998
			EP 0869847 A1	14-10-1998
			WO 9635413 A1	14-11-1996
			WO 9635516 A1	14-11-1996
			GB 2316086 A ,B	18-02-1998
			GB 2316342 A ,B	25-02-1998
			GB 2336551 A ,B	27-10-1999
			GB 2333975 A ,B	11-08-1999
			HU 9901981 A2	28-10-1999
			JP 11505530 T	21-05-1999
			JP 11507292 T	29-06-1999
			NO 975131 A	09-01-1998
			NO 975132 A	09-01-1998
			PL 323314 A1	16-03-1998
			PL 323315 A1	16-03-1998
			TR 9701323 T1	21-02-1998
			TR 9701324 T1	21-04-1998
			US 2002034592 A1	21-03-2002
			US 6406738 B1	18-06-2002
EP 0365123	B	25-04-1990	AT 110262 T	15-09-1994
			AU 4218489 A	23-03-1990
			CA 1339079 A1	29-07-1997
			DE 68917677 D1	29-09-1994
			DE 68917677 T2	22-12-1994
			EP 0365123 A1	25-04-1990
			ES 2058543 T3	01-11-1994
			WO 9001925 A1	08-03-1990
			GB 2222948 A ,B	28-03-1990
			IE 63764 B1	14-06-1995
			US 5004614 A	02-04-1991

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/03286

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5470603	A	28-11-1995	GB 2253164 A	02-09-1992
			AT 126431 T	15-09-1995
			AU 653989 B2	20-10-1994
			AU 1208492 A	15-09-1992
			CA 2081921 A1	23-08-1992
			CZ 9203434 A3	11-08-1993
			DE 69204127 D1	21-09-1995
			DE 69204127 T2	04-04-1996
			DK 526606 T3	27-12-1995
			EP 0526606 A1	10-02-1993
			ES 2078036 T3	01-12-1995
			WO 9214451 A1	03-09-1992
			GR 3018080 T3	29-02-1996
			HU 66848 A2	30-01-1995
			JP 2919971 B2	19-07-1999
			JP 5508337 T	25-11-1993
			PL 296624 A1	02-11-1993
			US 5656080 A	12-08-1997
US 5681583	A	28-10-1997	IT 1264696 B1	04-10-1996
			EP 0659074 A1	28-06-1995
			CA 2144167 A1	19-01-1995
			WO 9501781 A1	19-01-1995
			IL 109512 A	16-07-2000